Remarks

Duplicate Claims. Applicant was advised that should Claim 16 be found allowable, Claim 20 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Applicant has amended Claim 20 to particularly point out and distinctly claim a method of stabilizingly and structurally modifying 5-aminosalicylic acid in a manner that enhances its retention in the gastrointestinal tract and decreases the transfer of said acid from the lumen of the gastrointestinal tract to the systemic circulation of a subject comprising covalently conjugating the nitrogen atom of the amino group of 5-amino salicylic acid to a reducing sugar; a poly(ethylene glycol)-containing residue; or a poly(ethylene glycol) chain-containing tether wherein Z is lipoic acid. This restriction renders Claim 20 different from Claim 16, in which Z is a drug or therapeutic agent that is selected from the group consisting of lipoic acid, immunomodulators, antibacterials, and antioxidants (Claim 16).

Rejections Under 35 USC §112. (Sections numbered 5 and 6 of the Office Action) Claims 1-7, 9, 12-14, 16, and 19 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Each of claims 1-7, 9, 13, 16, and 19 contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Claims 1-7, 9, 13, 16 and 19 were amended to recite that "R is a sugar, with the exception that the sugar is not D-glucose;" however, the instant specification discloses that "R may be a 1-deoxy-D-glucose." Likewise, each of claims 12-14 was broadened by changing the passage "pharmacologically active moiety having a molecular weight that is less than about 1000 Daltons" to recite "drug or therapeutic agent" which reads on compounds not supported in the instant specification.

Applicant has amended claims 1-7, 9, 13, 16, and 19 to recite that R is a reducing sugar that is selected from the group consisting of galactose, fucose, fructose, N-acetylglucosamine, N-acetylgalactosamine, maltobiose, lactobiose, cellobiose, and N,N-diacetylchitobiose, wherein a covalent bond to the oxygen of a hydroxyl group originally substituted on the reducing sugar has been replaced by a covalent bond to the nitrogen of the amino group of the 5-aminosalicylic acid derivative. In pages 10 and 11 of the instant specification, Applicant has disclosed each of these reducing sugars and the manner in which the sugar residue is covalently joined to the amino group of 5-aminosalicylic acid.

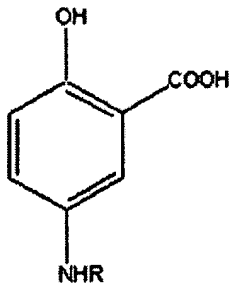
Likewise, Applicant has amended Claims 12-14 to recite that Z is a drug or therapeutic agent having a molecular weight that is less than about 1000 Daltons. The terms "drug" and "therapeutic agent" have been defined by Applicant on page 8, lines 14-22, of the instant specification. Further, the instant specification discloses on page 10, lines 5-6, that a "drug" is exemplified by an immunomodulator, antibacterial, or antioxidant, or other pharmacologically active agent, and on page 12, lines 8-11, that substituents Z encompass pharmacological agents having a molecular weight that is less than about 1000 Daltons.

Rejections Under 35 U.S.C. 112, Second Paragraph. (Section 8 of the Office Action) Claims 11, 14 and 15 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11, line 7, recites a process step that involves alkylating the amino group of 5-aminosalicylic acid with a poly(ethylene glycol) chain having an aldehydes or halide substituents on at least one terminus. However, the term "alkylating" was defined by the Examiner to mean the substitution of an alkyl group for a hydrogen atom in a cyclic compound. Applicant

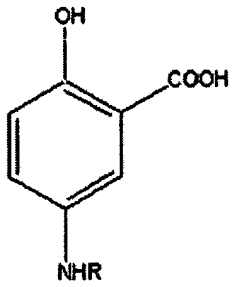
respectfully submits photocopies of the cover page from the book by Richard C. Larock entitled "Comprehensive Organic Transformations: A Guide to Functional Group Preparations Second Edition" (Wiley-VCH, New York, 1999) and page 789 of this textbook. In the equation at the top of the latter page, Larock discusses reactions which result in alkylation on nitrogen, a process in which an alkyl group (R') is substituted for hydrogen on an amine (i.e., R_2NH --> R_2NR'). In addition, at the bottom of the latter page, Larock refers the reader to page 779 for alkylation of amines by alkyl halides, of which a poly(ethylene glycol) chain having a halide substituent on at least one terminus would be an example. Further, on page 835, Larock discusses alkylation of amines using aldehydes, of which a poly(ethylene glycol) chain having an aldehyde substituent on at least one terminus would be an example. Applicant respectfully submits that these photocopies illustrate that one skilled in the relevant art will understand that the term "alkylation" encompasses reactions in which an alkyl group is substituted for hydrogen on an amine. In view of this, Applicant respectfully requests examination of Claim 11, as amended.

In Claim 14, line 5, the phrase "general formula (I)" lacks clear antecedent basis, since a "formula (I)" was not disclosed in the claim. Applicant has amended Claim 14 to particularly point out and distinctly claim the subject matter which applicant regards as her invention by providing in Claim 14 a therapeutic 5-aminosalicylic acid derivative composition having the general formula:



wherein R is a sugar, a poly(ethylene glycol)-containing residue, or a poly(ethylene glycol) chain-containing tether joining the amino group of 5-aminosalicylic acid at one terminus of the tether and a drug or therapeutic agent at the other terminus of the tether. The specification of the instant application discloses said therapeutic 5-aminosalicylic acid compositions on pages 10 and 11, for example.

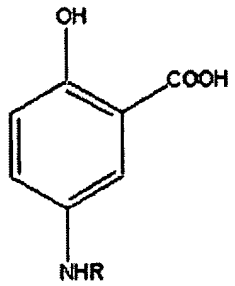
Claim 15 was incomplete because the preamble of the claim is drawn to a method of prophylactically or interventionally delivering 5-aminosalicylic acid to the gastrointestinal tract, but the body of the claim only discloses a description of the 5-aminosalicylic acid derivative composition and does not set forth a specific type of delivery process as proffered in the preamble of the claim. Applicant has amended Claim 15 to particularly point out and distinctly claim the subject matter which applicant regards as her invention by providing a method for delivering 5-aminosalicylic acid to the gastrointestinal tract of a subject comprising administering to the subject a pharmaceutical formulation comprising an effective amount of a therapeutic 5-aminosalicylic acid derivative composition having the general formula:



wherein R is a sugar, a poly(ethylene glycol)-containing residue, or a poly(ethylene glycol) chain-containing tether joining the amino group of 5-aminosalicylic acid at one terminus of the tether and a drug or therapeutic agent at the other terminus of the tether; and a pharmaceutical carrier.

Rejections Under 35 U.S.C. 102(b). (Sections 4 and 5 of the Office Action) Claims 1-3, 5, 6, 13, and 16-20 stand rejected under 35 U.S.C. 102(b) as being anticipated by Tjoernelund *et al.* (*Journal of Chromatography*, "Stability of 5-Aminosalicylic Acid and Its Metabolites in Plasma at -20°C: Formation of N—D-Glucopyranosyl-5-Aminosalicylic Acid," Vol. 570, No. 1, pp. 224-228, 1991). Applicant has amended Claims 1-3, 5, 6, 13, and 16-20 to recite that R is a reducing sugar that is selected from the group consisting of galactose, fucose, fructose, N-acetylglucosamine, N-acetylgalactosamine, maltobiose, lactobiose, cellobiose, and N,N-diacetylchitobiose, wherein a covalent bond to the oxygen of a hydroxyl group originally substituted on the reducing sugar has been replaced by a covalent bond to the nitrogen of the amino group of the 5-aminosalicylic acid derivative. Each of the reducing sugars in this group is disclosed in the instant application (e.g., on pages 10 and 11).

In her present invention Applicant discloses her surprising discovery of novel, therapeutic 5-aminosalicylic acid derivative compositions having the general formula



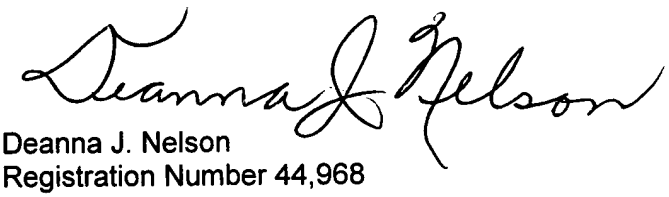
wherein R is a sugar, a poly(ethylene glycol)-containing residue, or a poly(ethylene glycol) chain-containing tether joining the amino group of 5-aminosalicylic acid at one terminus of the tether and a drug or therapeutic agent at the other terminus of the tether. In contrast to 5-aminosalicylic acid and its acylated derivatives, each of which is rapidly and extensively transferred from the gastrointestinal tract to the systemic circulation, the oxygen-containing alkyl substituents on the amino group of 5-aminosalicylic acid derivative compositions of her invention introduce physico-chemical characteristics that enable retention of the derivative

compositions in the gastrointestinal tract and delivery of these anti-inflammatory derivative compositions to inflamed tissue sites in that organ. Further, Applicant has unexpectedly discovered a novel method of delivery of 5-aminosalicylic acid to the gastrointestinal tract following oral administration of said 5-aminosalicylic acid derivative compositions in pharmaceutical preparations and to pharmaceutical compositions containing the therapeutic 5-aminosalicylic acid derivative compositions of her present invention, in that the derivative compositions of her invention retain the electron densities and related anti-inflammatory activity at each functional group that are found in 5-aminosalicylic acid. In contrast, acylated derivatives of 5-aminosalicylic acid that are known in the art are deactivated by acylation and are no longer active as anti-inflammatory agents. Likewise, Applicant has unexpectedly discovered that the therapeutic 5-aminosalicylic acid derivative compositions of her invention are stabilized by the sugar or poly(ethylene glycol) containing alkyl groups on the amino group of 5-aminosalicylic acid of compositions of her invention in a manner that will enhance the retention of said compositions in the intestine, decrease the cellular absorption thereof, and decrease the transfer of said compositions or the 5-aminosalicylic acid derived therefrom to the systemic circulation. Her invention is based upon her unexpected discovery that the topical delivery of therapeutically effective amounts of therapeutic 5-aminosalicylic acid derivative compositions of her invention to the gastrointestinal tract following oral administration in a pharmaceutically acceptable dosage form enables significant advances in the medical arts, particularly in the treatment of inflammatory bowel diseases. Until her disclosures in the instant application, no 5-aminosalicylic acid compound was retained sufficiently to enable delivery of the anti-inflammatory 5-aminosalicylic acid to inflamed sites in the intestine.

In view of the foregoing, Applicant respectfully submits that the claims to her invention, as amended, are in condition for allowance and respectfully requests reconsideration thereof.

Should additional information be required, Deanna J. Nelson is representing Applicant before the Office. She is available by telephone at (919) 678-9478 during the hours of 8:00 AM to 4:00 PM Monday through Friday and by facsimile at (919) 678-9474.

Respectfully submitted,



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Registration Number 44,968

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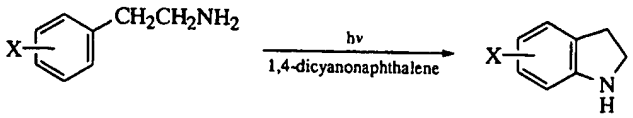
2. Alkylation on Nitrogen

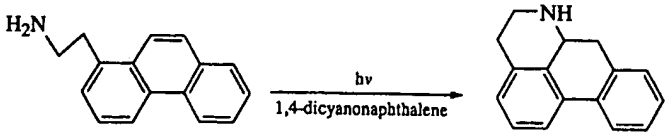
See also page 779, Section 4; page 831, Section 9; and page 835, Section 10.

$R_2NH \longrightarrow R_2NR'$	
$PhCHN_2$, cat HBF_4	TL *30* 4759 (1989)
$RCH{=}CHC(N_2)CO_2R$, cat $Rh_2(OAc)_2$ ($R' = RCH{=}CHCHCO_2R$)	SL 1191 (1995)
$[(R'O)_3PCH_3]BF_4$	JOC *49* 4877 (1984)
R'_2CuLi, O_2	JOC *45* 2739 (1980)
$PhI(OTf)CH_2CF_3$; 2,4,6-collidine ($R' = CH_2CF_3$)	TL *35* 8015 (1994)
$RC{\equiv}C^{+}CHR\ BF_4^-$ ($Co_2(CO)_6$)	TL *34* 2919 (1993)
$RC{\equiv}CCHROH, BF_3{\cdot}OEt_2$ ($Co_2(CO)_6$)	TL *36* 2823 (1995)
$(Ar_2I)X$, cat $Cu(OAc)_2$ ($R' = Ar$)	JOC *45* 2127 (1980)
$p\text{-}C_6H_4(NO_2)_2$ ($R' = p\text{-}C_6H_4NO_2$)	CL 31 (1986)
R'_3Bi, cat $Cu(OAc)_2$ ($R' = 1°$ alkyl)	TL *29* 857 (1988)
Ph_2BiR', cat $Cu(OAc)_2$ ($R' = 1°$ alkyl)	TL *29* 857 (1988)
Ph_3Bi, cat $Cu(OAc)_2$ ($R' = Ph$)	TL *28* 887 (1987)
$Ph_3Bi(OAc)_2$, cat Cu ($R' = Ph$)	TL *27* 3615 (1986); *30* 937 (1989)
$Ph_3Bi(OAc)_2$, cat $Cu(OAc)_2$ ($R' = Ph$)	J Gen Chem USSR *55* 413, 2232 (1985) TL *30* 937 (1989)
$Ph_3Bi(OAc)_2$, cat $Cu(O_2CCF_3)_2$ ($R' = Ph$)	TL *30* 937 (1989)
$ArPb(OAc)_3$, cat $Cu(OAc)_2$ or $Cu(O_2CCF_3)_2$ ($R' = Ar$)	TL *28* 3111 (1987); *30* 1377 (1989)

For alkylation or arylation by alkyl/aryl halides or sulfonates, see page 779, Section 4.



TL *31* 5373 (1990)



TL *35* 535 (1994)